

About the inhibiting mechanism in the growth of conjunctive tissue produced by cortisone.

The experimental observations of patients performed thus far indicate that cortisone as an inhibiting effect on scarring. (Thorn<sup>1</sup>, Baker and Whitaker<sup>2</sup>, Blunt et al<sup>3</sup>, Schiller<sup>4</sup>, Ragan<sup>5</sup>). Some findings lean to the conclusion that this effect is the result not only of local applications but of general applications as well. Due to the type of experiment carried out, it cannot be stated with certainty whether the elements of the conjunctive tissue are exclusively responsible for these effects nor if the direct effect appears in the case of a local application regardless of the general effects of the cortisone. In order to clarify this question, it was necessary to formulate a method which takes both of these conditions into consideration. After various preliminary trials, the granuloma of foreign matter generated in a certain way was identified as suitable for such treatment. In order to answer the question mentioned above, experiments were performed with the help of this method. On one hand, these experiments determined the growth of the granuloma in the presence of general applications of cortisone; and on the other hand the growth produced when the foreign matter which generated the granuloma was impregnated with cortisone. In the latter, an unimpregnated foreign body was used as a control of the general effects.

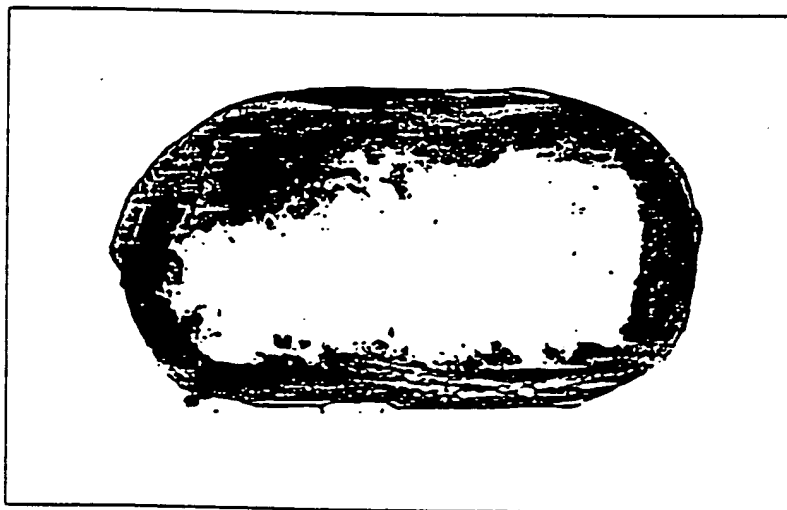


Fig. 1a: Raw cotton granuloma 6 days after subcutaneous implantation. Untreated control rats. Haemalaun-Eosin 10x.

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- <sup>1</sup> G.W. Thorn. Proceed. Laurentian Hormon Conf. Vol. IV, 1949 (Academic Press, N.Y. City).  
<sup>2</sup> B.L. Baker und W.L. Whitaker, Anat. Rec. 102, 333 (1948); Endocrin. 46, 544 (1950).  
<sup>3</sup> W.J. Blunt und Mitarbeiter, Proc. Soc. exp. Biol. 73, 678 (1950).  
<sup>4</sup> K. Schiller und H.A. Baxter, Ann. Meeting Med. Chir. Soc. Montreal (1950).  
<sup>5</sup> CH. Ragan und Mitarbeiter, Proc. Soc. exp. Biol. 72, 718 (1949).

On implanting a pressed piece of cotton of a certain size and weight into a rat, characteristic granulomas are obtained a short time later, as can be seen in the table below (Figure 1). The histological analysis demonstrates that these are composed of non-differentiated conjunctive tissue and gigantic cells which display a relatively high degree of mitosis.

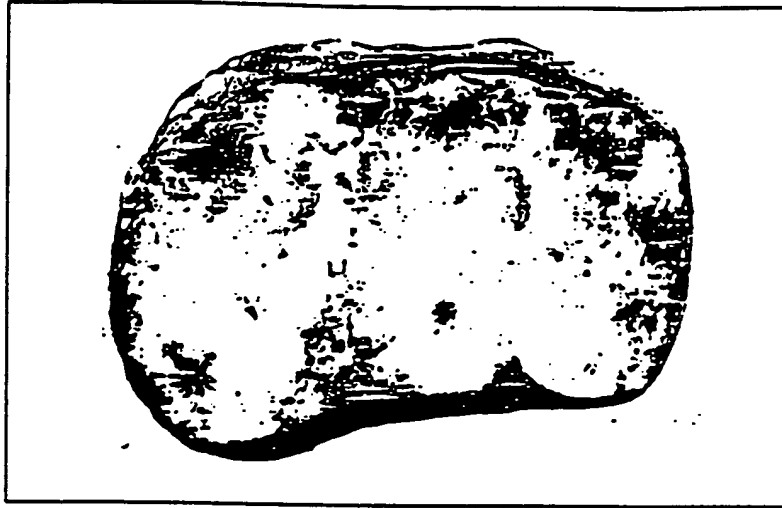


Fig. 1b: Raw cotton granuloma 6 days after subcutaneous implantation. Animal treated with cortisone (10 mg/kg/day s.c.) Haemalaun-Eosin 10x. (Most of the cotton was detached from the rest during histological treatment).

When quantiles of cortisone are applied daily to the animals, an inhibition in the excrescence of the conjunctive tissue is observed which is directly proportional to the amount of cortisone administered. Where sufficiently high doses of cortisone are applied there is a pronounced inhibition in the growth of the conjunctive tissue (Figure 2).

Where increased amounts of cortisone are administered, disturbances of a general nature such as growth inhibition, negative nitrogen balance, etc. arise as a consequence of the effects of the cortisone; these phenomena have been described on several occasions (Baker<sup>1</sup>, Stoerk and Porter <sup>2</sup>, Ingie and Prestrud<sup>3</sup>). The comparison of the magnitude of growth inhibition with the growth inhibition of the conjunctive tissue proves that the intensity of the effect on the growth and the excrescence of the conjunctive tissue is equally pronounced. (Fig. 3)

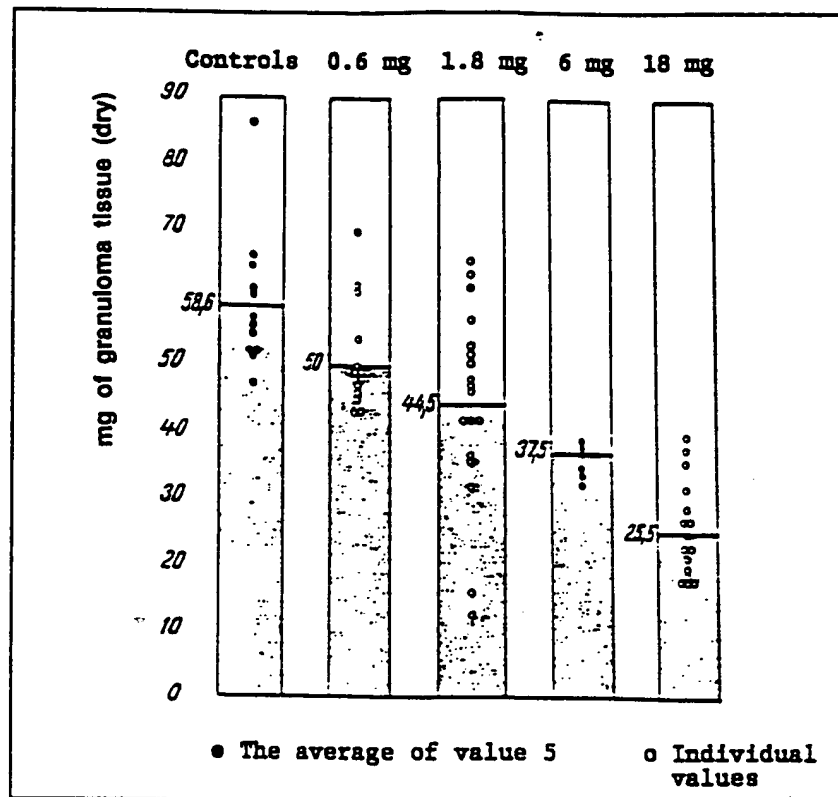


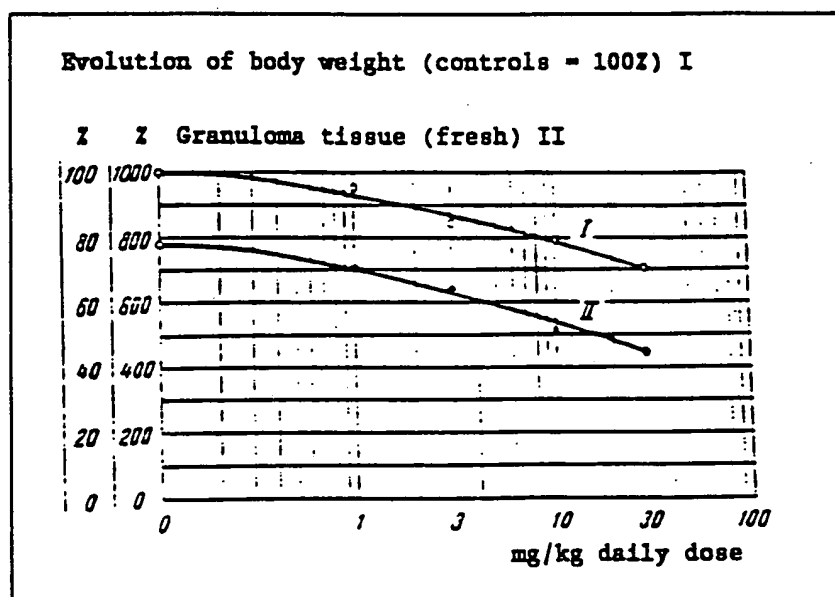
Fig. 2: Weights of the granuloma after the different amounts cortisone (general treatment).

Table 1  
Comparison of the weight of the grafts following general of localized treatment with cortisone, respectively.

Total amount administered in mg	General treatment	Localized treatment	
	average value of the 2 grafts	Impregnated graft	Control graft
Control	100	100	100
0.1	-	75	114
0.6	85	-	-
1	-	41	90
1.8	76	-	-
6	64	-	-
10	-	-2	85

<sup>1</sup> B.L. Baker. Symposium on the Adrenal Cortex. Ann. Meeting AAAS. (1949)  
<sup>2</sup> H.C. Stoerk und C.C. Porter. Proc. Soc. Exp. Biol. 74, 65 (1950)  
<sup>3</sup> D.J. Ingle und M.C. Prestrud, Endocrinology, 45, 143 (1949).

However, the proof or the exclusion of the local effects of cortisone on the growth of the conjunctive tissue require special attention in order to further clarify the mechanism of the action. On determining the generation of granuloma in rats which have been implanted with pressed pieces of cotton on the right and left sides of the body, with only one of the two pieces impregnated with cortisone, a considerably stronger inhibiting effect is observed in relation to the pressed piece of cotton impregnated with cortisone. In the case of the corresponding dosage, significant inhibition of the growth of the conjunctive tissue around the impregnated cotton can be provoked without any clear effects of the second piece of pressed cotton being evident (Table 1). Naturally, the concentration of cortisone around the impregnated piece of cotton cannot be demonstrated. Only when is possible will it be possible to deduce the complete identity with a specific situation in the case of general applications.



**Fig. 3: Effects of the different dose of cortisone on the weight of the granuloma and body weight. Coordinates: I Percentage of change in animal's body weight. The weight at the beginning of the experiment = 100%. II Percentage of increase in the weight of the pressed piece of grafted cotton. The weight before implantation = 100%.**

If 3.0 or 30.0 mg/kg of cortisone are administered daily and on a general basis, the same effects are obtained as with 0.1 or 1.0 mg of cortisone impregnating a foreign body. The weight of the foreign body impregnated or its volume in relation to the weight of the animal is: 1:250. The ratio resulting from the doses of local concentration indicated above is 1:30. Considering the diversity of the reabsorption and of the distribution in the case of a local and general application, the ratio should be greater if the average active concentration is estimated, and in this way we would be closer to finding the ratio between "animal size: granuloma size".

It can be deduced from these findings that cortisone provokes an inhibition in the growth of conjunctive tissue, whether administered generally or locally in similar concentrations.

It appears that there is a mechanism which inhibits the growth of the conjunctive tissue in the case of both general and local cortisone applications.

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Scientific Laboratories of the Company "Ciba". Basilea, October 13, 1950.

#### **Summary**

A method is described which makes quantitative studies of the action of cortisone on connective tissue possible. Foreign body granulomas are provoked in rats by subcutaneous implantation of pellets of compressed cotton. Application of cortisone results in a diminution of granuloma formation, which can be expressed quantitatively by determining the fresh and the dry weight. Cortisone was effective by local as well as by general application, similar concentrations producing the same degree of inhibition of connective tissue.

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